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High Sensitivity C-Reactive Protein, Tumor Necrosis Factor-α, Interleukin-6, and Vascular Cell Adhesion Molecule-1 Levels in Asian Indians with Metabolic Syndrome and Insulin Resistance (CURES-105)

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Abstract

Aim:

The aim of this study was to assess levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1) in South Indian subjects with and without MS and among MS subjects with and without insulin resistance (IR).

Methodology:

From the population-based Chennai Urban Rural Epidemiology Study, 334 subjects with MS and 342 subjects without MS were selected. Metabolic syndrome was diagnosed based on modified National Cholesterol Education Program criteria. High-sensitivity C-reactive protein, TNF-α, IL-6, and VCAM-1 were measured by enzyme-linked immunosorbent assay. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR) using the following formula: fasting insulin (μIU/ml) × fasting glucose (mmol/liter)/22.5.

Results:

Subjects with MS had significantly higher levels of all four inflammatory markers compared to those without MS: hs-CRP (2.57 vs 2.19 mg/liter) ($p < .05$), TNF-α (4.47 vs 3.89 pg/ml) ($p < .05$), IL-6 (16.22 vs 10.96 pg/ml) ($p < .05$), and VCAM-1 (13.8 vs 7.94 pg/ml) ($p < .05$). In the total study subjects, hs-CRP ($r = 0.089$, $p = .047$), TNF-α ($r = 0.113$, $p = .040$), IL-6 ($r = 0.176$, $p = .042$), and VCAM-1 ($r = 0.230$, $p = .06$) were significantly correlated with MS. With increasing quartiles of IR, mean levels of hs-CRP (p for trend <.001) and TNF-α (p for trend <.05) increased linearly. MS subjects with IR had higher levels of hs-CRP ($p < .001$) and TNF-α ($p < .05$) compared to MS subjects without IR.

Conclusion:

In Asian Indians, inflammatory cytokines hs-CRP, TNF-α, IL-6, and VCAM-1 are elevated in subjects with MS while hs-CRP and TNF-α are further elevated in those with MS and IR.

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Abbreviations: (CURES) Chennai Urban Rural Epidemiological Study, (CV) coefficient of variation, (CVD) cardiovascular disease, (CI) confidence interval, (HbA1c) hemoglobin A1c, (HDL-C) high-density lipoprotein cholesterol, (HOMA-IR) homeostasis model assessment of insulin resistance, (hs-CRP) high-sensitivity C-reactive protein, (IL-6) interleukin-6, (IR) insulin resistance, (LDL-C) low-density lipoprotein cholesterol, (MS) metabolic syndrome, (NCEP) National Cholesterol Education Program, (OR) odds ratio, (TNF-α) tumor necrosis factor-α, (VCAM-1) vascular cell adhesion molecule-1

Keywords: Asian Indians, hs-CRP, IL-6, inflammation, metabolic syndrome, South Asians, TNF-α, type 2 diabetes, VCAM-1

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Introduction

Metabolic syndrome (MS) refers to the clustering of cardiovascular risk factors that include obesity, dyslipidemia, and hypertension.[1] The syndrome is heterogeneous and has significant impact on glucose and fat metabolism and cellular growth and differentiation.[2] It is estimated that people with MS have a two-fold risk of developing cardiovascular disease compared to those without MS, and a five-fold increased risk of developing type 2 diabetes.[3,4] Insulin resistance (IR) is believed to be a key pathogenic factor for MS and central obesity, the principal clinical manifestation.[5]

Low-grade inflammation has been hypothesized to be involved in the pathogenesis of MS.[6] There is also evidence that chronic inflammation may induce IR.[7] Another hypothesis states that inflammatory processes could be induced by metabolic alterations in glucose and lipids.[8] Asian Indians have an increased susceptibility to type 2 diabetes[9] and greater insulin resistance[10,11] associated with hyperinsulinemia.[12] We have also reported on the relationship between inflammatory markers and glucose intolerance.[13]

The present study was undertaken to assess the relationship of some of the systemic and vascular inflammatory markers, namely high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1) in subjects with and without MS and among MS subjects with and without IR.

Research Design and Methods

Study subjects were recruited from the Chennai Urban Rural Epidemiological Study (CURES), an ongoing epidemiological study conducted on a representative population (aged ≥20 years) of Chennai (formerly Madras), the fourth largest city in India. The methodology of the study has been published elsewhere.[14] Details of the sampling are described on our website (http://www.mdrf.in/misc/CURES.pdf). Briefly, in Phase 1 of the urban component of CURES, a total of 26,001 individuals were recruited based on a systematic random sampling technique. Self-reported diabetic subjects (physician-diagnosed) were classified as known diabetic subjects. In Phase 2 of CURES, all known diabetic subjects (n = 1529) were invited to our center for detailed studies on vascular complications.

The subjects for this study were randomly selected using computer-generated numbers from Phase 2 of CURES and comprised the following: subjects with MS (n = 334) and subjects without MS (n = 342). Institutional ethical committee approval was obtained from the Madras Diabetes Research Foundation Ethical Committee and written informed consent was obtained from all study subjects. The exclusion criteria included previous history of any chronic disease, including kidney or liver disease or any inflammatory disorders.

Anthropometric Measurements

Anthropometric measurements, including weight, height, and waist circumference, were obtained using standardized techniques as detailed elsewhere.[14] Height was measured with a stadiometer. Weight was measured with a traditional spring balance that was kept on a firm horizontal surface. Waist circumference was measured using a nonstretchable fiber measuring tape. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the right arm in the sitting position to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and the mean of the two was taken as the blood pressure.

Biochemical Parameters

Fasting plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and high-density lipoprotein cholesterol (HDL-C) (polyethylene glycol-pretreated enzymes direct method) were measured using a Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany). The intra- and interassay coefficient of variation (CV) for the biochemical assays ranged between 3.1 and 7.6%. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.[15] Glycosylated hemoglobin A1c (HbA1c) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA). The intra- and interassay CV of HbA1c was less than 10%.

Insulin resistance was calculated using the homeostasis model assessment of IR (HOMA-IR) with the following

formula: (μIU/ml) fasting glucose × (mmol/liter)/22.5. Subjects whose HOMA-IR values exceeded the 75th percentile of the total population (i.e., 2.58) were considered to have IR.[16]

C-reactive proteins (BioCheck, Foster City, CA; intra- and interassay CV of 4.0 and 7.8%, respectively), IL-6 (R&D Systems, Minneapolis, MN; intra- and interassay CV of 3.2 and 6.0%, respectively), VCAM-1 (BioSource International, Camarillo, CA; intra- and interassay CV of 3.0 and 5.3%, respectively), and TNF-α concentrations were measured by enzyme-linked immunosorbent assay (Biosource, Europe). In-kit quality control was within acceptable range (CV: 3.3–6.9%). The intra and inter-assay CV ranged between 3.4 and 7.7%.

Definitions

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria[17] modified for waist according to World Health Organization Asia Pacific guidelines for obesity.[18] Metabolic syndrome was defined as the presence of any three of the following abnormalities: abdominal obesity defined as waist circumference of at least 90 cm for men and at least 80 cm for women, high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg), elevated fasting glucose (fasting plasma glucose ≥100 mg/dl), hypertriglyceridemia (≥150 mg/dl), or low HDL-C [<40 mg/dl (male), <50 mg/dl (female)].

Statistical Analysis

One-way analysis of variance or Student's *t*-test, as appropriate, was used to compare groups for continuous variables. Chi-square test or Fisher's exact test, as appropriate, was used to compare proportions. Triglycerides, HOMA-IR, hs-CRP, VCAM-1, TNF-α, and IL-6 values were log-transformed to obtain a normal distribution. Pearson correlation analysis was performed to examine the association of various cardiovascular risk factors with inflammatory markers and adhesion molecules. All analyses were done using Windows-based SPSS statistical package (version 15.0, Chicago, IL), and *p* values of ≤.05 were taken as the level of significance.

Results

The clinical and biochemical profiles of the study subjects are shown in **Table 1**. **Figure 1** shows that subjects with MS had significantly higher levels of hs-CRP and TNF-α compared to those without MS: hs-CRP (2.57 vs 2.19 mg/liter) ($p < .05$), TNF-α (4.47 vs 3.89 pg/ml) ($p < .05$). **Figure 2** shows that IL-6 (16.22 vs 10.96 pg/ml) ($p < .05$) and VCAM-1 (13.8 vs 7.94 pg/ml) ($p < .05$) are significantly higher in those with MS than those without MS.

Table 1.
Clinical Parameters of Subjects With and Without Metabolic Syndrome

Parameters	NonMS subjects (n = 342)	MS subjects (n = 334)	p value
Age (years)	49.1 ± 11.3	49.3 ± 11.3	.807
Body mass index (kg/m^2)	21.3 ± 3.8	25.6 ± 4.2	<.001
Waist circumference (cm)	77.4 ± 10.5	91.4 ± 9.6	<.001
Systolic blood pressure (mm Hg)	115 ± 16	130 ± 21	<.001
Diastolic blood pressure (mm Hg)	70 ± 10	78 ± 11	<.001
Fasting plasma glucose (mg/dl)	100 ± 36	141 ± 73	<.001
HbA1c (%)	6.9 ± 1.9	7 ± 2.1	.491
Total cholesterol (mg/dl)	176 ± 36	199 ± 42	<.01
Log triglycerides (mg/dl)	89 ± 1.5	165.9 ± 1.7	<.001
HDL-C (mg/dl)	48.8 ± 10.8	40.4 ± 8.3	<.001
LDL-C (mg/dl)	117 ± 34	120 ± 38	.339
HOMA-IR	2.91 ± 2.12	3.03 ± 2.13	.601

Figure 3 shows that MS subjects with IR had higher levels of hs-CRP ($p < .001$) and TNF-α ($p < .05$) compared to MS subjects without IR.

Table 2 shows that, with increasing quartiles of IR, mean levels of hs-CRP (p for trend <.001) and TNF-α (p for trend <.05) increased linearly.

Table 3 shows the Pearson correlation analysis of the markers with MS and IR. In the total study subjects, hs-CRP ($r = 0.089$, $p = .047$), TNF-α ($r = 0.113$, $p = .040$), IL-6 ($r = 0.176$, $p = .042$), and VCAM-1 ($r = 0.230$, $p = .06$) were significantly correlated with MS. Hs-CRP ($r = 0.247$, $p = .000$) and TNF-α ($r = 0.126$, $p = .022$) showed a positive correlation with IR.

Table 4 shows the results of linear regression analysis of the inflammatory markers using MS as the dependent variable. TNF-α [odds ratio (OR): 2.9, confidence interval

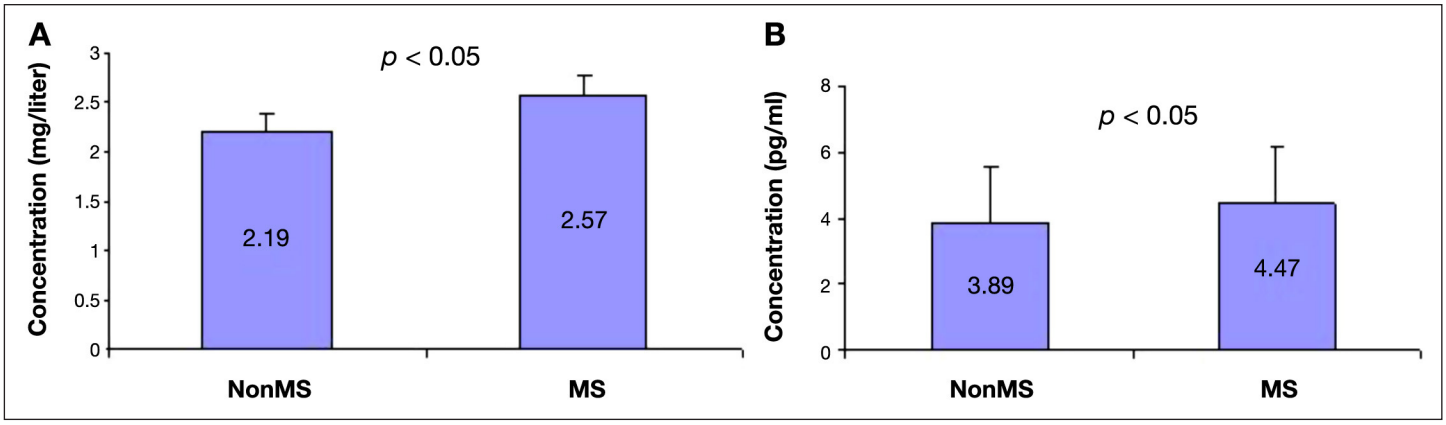

Figure 1. (A) Levels of hs-CRP in MS and nonMS subjects. **(B)** Levels of TNF-α in MS and nonMS subjects.

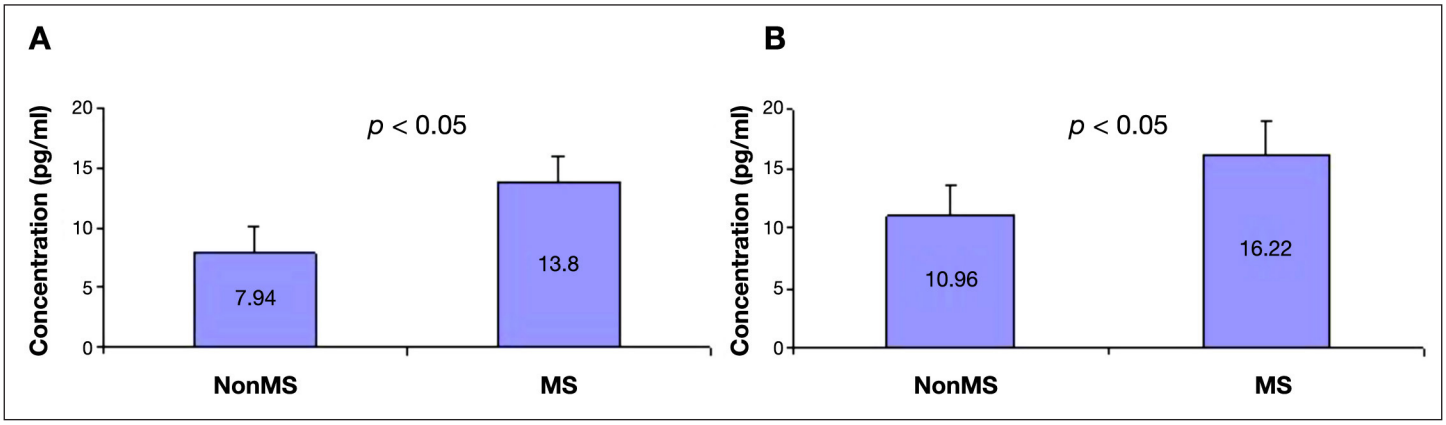

Figure 2. (A) Levels of VCAM-1 in MS and nonMS subjects. **(B)** Levels of IL-6 in MS and nonMS subjects.

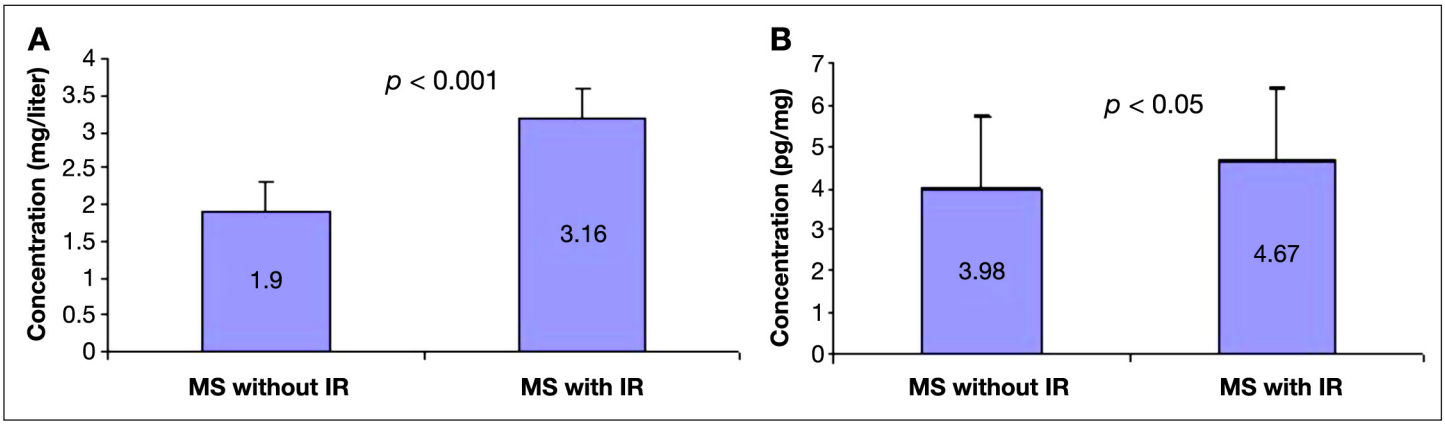

Figure 3. (A) Levels of hs-CRP in MS subjects with and without IR. **(B)** Levels of TNF-α in MS subjects with and without IR.

Table 2.
Levels of the Inflammatory Markers in Quartiles of Insulin Resistance

Inflammatory markers	Q1 (<1.30) (*n* = 118)	Q2 (1.30–2.40) (*n* = 113)	Q3 (2.40–4.0) (*n* = 119)	Q4 (>4.0) (*n* = 122)	*p* value
Log hs-CRP (mg/liter)	1.51 ± 2.88	2.34 ± 2.45	2.45 ± 2.63	3.80 ± 2.04	<.001
Log TNF-α (pg/mg)	3.98 ± 1.82	3.98 ± 1.70	4.17 ± 1.66	4.90 ± 1.70	<.05
Log IL-6 (pg/ml)	15.85 ± 2.4	14.13 ± 2.88	13.18 ± 2.8	17.78 ± 2.51	.52
Log VCAM-1 (pg/ml)	12.59 ± 2.51	10.96 ± 2.63	10.72 ± 2.69	12.02 ± 2.63	.62

(CI): 1.00–8.43, $p < .05$], IL-6 (OR: 3.65; CI: 1.20–11.08; $p < .05$), and VCAM-1 (OR: 4.23; CI: 1.20–14.85; $p < .05$) showed a significant association even after adjustment for age and gender whereas the association with hs-CRP was lost when gender was introduced into the model.

Table 5 shows the results of linear regression analysis of the inflammatory markers with IR as the dependent variable. Hs-CRP (OR: 3.35; CI: 2.08–5.40; $p < .001$) and TNF-α (OR: 3.08; CI: 1.19–7.96; $p < .05$) showed a significant association with IR even after adjusting for age and gender; however the association of IL-6 and VCAM-1 with IR was lost after adjusting for age and gender.

Table 3.
Pearson Correlation of the Inflammatory Markers with MS and IR[a]

Parameters	MS		IR	
	r value	*p* value	*r* value	*p* value
Log hs-CRP	0.089	**.047**	0.247	**.000**
Log TNF-α	0.113	**.040**	0.126	**.022**
Log IL-6	0.176	**.042**	0.064	.460
Log VCAM-1	0.230	**.006**	0.078	.357

[a] *p* values in bold font emphasize correlation.

Discussion

The main findings of this study are as follows: (1) levels of inflammatory markers hs-CRP, TNF-α, IL-6, and VCAM-1 are higher in subjects with MS than those without; (2) there is a progressive increase in the levels of inflammatory markers with increasing quartiles of IR; (3) levels of hs-CRP and TNF-α are significantly higher in MS subjects with IR compared to those without; and (4) TNF-α, IL-6, and VCAM-1 are associated with MS, independent of age and gender, whereas hs-CRP and TNF-α are associated with IR, independent of age and gender.

Although inflammation has been demonstrated to play a role in metabolic disorders, the relative importance of the different inflammatory markers in MS needs to be explored further.[19] Also, clinical data on cell adhesion molecules is limited.[20] Moreover, there is very little data on Asian Indians who have increased IR and are at increased risk of premature coronary artery disease.[21]

Ridker and colleagues[22] and Rutter and colleagues[23] showed a significant association between serum concentrations of hs-CRP and various components of MS. Festa and colleagues[24] showed in the Insulin Resistance and Atherosclerosis Study study a positive correlation of hs-CRP

Table 4.
Logistic Regression Using MS as the Dependent Variable and Inflammatory Markers as Independent Variables

Inflammatory markers	Crude		Adjusted for age		Adjusted for age and gender	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Log hs-CRP	1.55 (1.00–2.39)	<.05	1.55 (1.00–2.41)	<.05	1.24 (0.78–1.96)	.358
Log TNF-α	2.78 (1.04–7.45)	<.05	2.90 (1.03–8.14)	<.05	2.91 (1.00–8.43)	<.05
Log IL-6	2.73 (1.01–7.34)	<.05	2.70 (1.00–7.25)	<.05	3.65 (1.20–11.08)	<.05
Log VCAM-1	4.73 (1.47–15.20)	<.05	4.92 (1.49–16.14)	<.05	4.23 (1.20–14.85)	<.05

Table 5.
Logistic Regression Using IR as the Dependent Variable and Inflammatory Markers as Independent Variables[a]

Inflammatory markers	Crude		Adjusted for age		Adjusted for age and gender	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Log hs-CRP	3.44 (2.16–5.46)	<.001	3.44 (2.19–5.58)	<.001	3.35 (2.08–5.40)	<.001
Log TNF-α	2.88 (1.16–7.15)	<.05	3.09 (1.20–7.97)	<.05	3.08 (1.19–7.96)	<.05
Log IL-6	1.39 (0.58–3.30)	.45	1.38 (0.58–3.30)	.46	1.48 (0.60–3.62)	.39
Log VCAM-1	1.46 (0.65–3.26)	.36	1.46 (0.65–3.26)	.35	1.34 (0.59–3.03)	.49

[a] Dependent variable: IR

with IR and other components of MS. Alterations in VCAM-1 in subjects with MS have been shown in other populations.[20,25] Our study results show agreement with these findings. In contrast, Vaverkova and colleagues[26] demonstrated VCAM-1 to have a positive association with adiponectin, a potential antiinflammatory adipocytokine in patients with cardiovascular disease (CVD) and dyslipidemia. The differences observed could be due to the differences in the stages of the disease, the ethnic group studied, and the age of the study subjects in the two studies.

Interleukin-6 and TNF-α have been found to be higher in subjects with MS and IR.[27] Tumor necrosis factor-α and IL-6 are important mediators of inflammation and could provide a potential link between visceral fat and systemic inflammation.[28] They are both known to promote lipolysis and the secretion of free fatty acids, which contribute to an increase in hepatic glucose output and IR, impair adipocyte differentiation, and promote inflammation. Both factors are released from the vessel wall during an inflammatory response and in turn stimulate the release of acute phase reactant hs-CRP, which induces the expression of VCAM-1.[29] VCAM-1 is believed to best reflect a proatherogenic state and there are animal studies that show an inhibition of inflammatory cell accumulation due to a reduction in the expression of VCAM-1.[30] *In vitro* studies using human cultured endothelial cells show that insulin at concentrations pathophysiologically relevant for IR states selectively promotes the expression of VCAM-1.[31] One possible mechanistic explanation for overproduction of adipokines is an increase in constitutive nuclear factor κB activity.[32] Tumor necrosis factor-α affects insulin sensitivity by altering the phosphorylation of insulin receptor substrate-1 and interferes with the insulin signaling cascade, thereby leading to IR.[33] Stress created in cells and organs by metabolic abnormalities seen in MS could lead to a surge in TNF-α and IL-6 levels, and consequent activation of inflammation might lead to diabetes and CVD.[33]

The link between inflammation, MS, and IR reflects an ongoing cytokine-mediated acute phase response. The results of this study highlight the importance of IR in aggravating inflammation in subjects with MS and suggest the role of inflammatory markers in MS. One of the limitations of the study is that it is a cross-sectional study, and does not elucidate on the causal roles of the various biomarkers studied. The strengths of this study are that it used a panel of inflammation markers (e.g., IL-6, hs-CRP, TNF-α, and VCAM-1) and that it is a population-based study in an ethnic group, who have high rates of diabetes and CVD, for which such information has not been readily available.

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